

REMARKS

Prior to entry of this Amendment, Claims 37-58, 60-75, and 77-80 were pending and under consideration, with Claims 40, 41, 54, 55 and 71-75 withdrawn from further examination as being drawn to non-elected inventions. With this Amendment, Claims 51-58, 60-75, and 77-80 have been cancelled, and Claims 37, 38, and 40 are being amended. Upon entry of these amendments, Claims 37-50 remain pending and under consideration.

I. Amendments to the Claims

Claims 51-58, 60-75, and 76-80 have been cancelled, without prejudice against their reintroduction into this or one or more timely-filed related applications.

Claim 37 has been amended to recite “functional” mast cells. Support for the amendment is found in the specification at least on page 15, lines 6-7. For consistency with this amendment, Claims 38 and 40 have been amended by deleting reference to specific mast cell types generated. The amendments do not introduce new matter. Entry is therefore requested.

II Claim Objections

Claim 66 is objected to as being an improper dependent claim. The objection is moot in light of the cancellation of this claim.

III Rejections Under 35 U.S.C. § 112, ¶ 2

Claims 51-53, 56-58, 60-66 stand rejected under 35 U.S.C. § 112 for indefiniteness with respect to “substantially pure” population of mast cells. Although Applicant disagrees with the propriety of the rejection for the reasons already of record, Applicant has cancelled the claims at issue in an effort to expedite the prosecution of this case. Thus, the rejection is moot.

IV Rejections Under 35 U.S.C. §§ 102(b) and 103(a)

Claims 51-53, 56-58, and 64-66 stand rejected as allegedly anticipated under 35 U.S.C. § 102(b) or as allegedly obvious under 35 U.S.C. § 103(a) over Saito et al., *Int Arch. Allergy Immunol* 107:63-65 (1995). The rejection is moot in light of the cancellation of the claims.

V Rejections Under 35 U.S.C. § 103(a)

A. Claims 51-53, 56-58, and 60-66

Claims 51-53, 56-58, and 60-66 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Kirshenbaum et al., *Blood* 94:2333-42 (1999). The rejection is moot in light of the cancellation of the claims.

B. Claims 37-39, 42-53, 56-58, and 60-66

Claims 37-39, 42-53, 56-58, and 60-66 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Saito et al., *J. Immunol.* 157:343-350 (1996) in view of Zhang, et al., *Chin. J. Biotechnol.* 15:189-94 (1999). The rejection is moot as applied to Claims 51-53, 56-58 and 60-66 and traversed with respect to Claims 37-39 and 42-50.

Applicant initially addresses certain Patent Office characterizations of Zhang that are contrary to the substance of its teachings. The Patent Office cites Zhang as describing the influence of flt-ligand (FL) on *ex vivo* expansion of mononuclear cells from cord blood, with IL-3 being an “indicator for population expansion potential.” This characterization of IL-3, however, is puzzling since Zhang is directed to examining the effect of FL on cell expansion with various combinations of cytokines, including IL-3. The presence of IL-3 does not define a maximum expansion potential of the cells. As can be seen in Figure 1 for different cytokine combinations containing IL-3, the fold expansion is dependent upon the presence of other cytokines and not just IL-3 + FL (*e.g.*, compare fold expansion with FL + SCF + IL-3 and FL + SCF + IL-3 + IL-6 + G + GM). Applicant requests clarification on this matter to better understand the reasoning behind the statement.

With respect to the Patent Office’s description of Zhang as teaching expansion of cells in excess of 10^{11} cells, Applicant has not been able to identify the source of this number and requests clarification on this point.

Turning to the substance of the rejection, an obviousness determination under §103(a) places the initial burden of establishing a *prima facie* case of obviousness on the Patent Office. See MPEP § 2142. To establish a *prima facie* case, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine their

teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference(s) must teach or suggest each and every limitation of the rejected claims. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not in Applicant's disclosure. See In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991); see also MPEP § 2142. If any *one* of these criteria is not met, *prima facie* obviousness is not established.

In the instant case, Claim 37 recites a method comprising culturing CD34+ cells in the presence of SCF and flt-3 ligand to generate a population of progenitor cells *and thereafter* culturing the population of progenitor cells in presence of SCF and a suitable cytokine to generate a population of functional mast cells. Thus, the claim recites a *multistep* culturing process, where progenitor cells are expanded in presence of an initial set of cytokine mixture and then further cultured in presence of a different set of cytokine mixture to generate a population of mast cells.

In contrast, Zhang teaches use of a single step method for generating CFU-GM producing cells from cord blood mononuclear cells, while Saito teaches use of a single step method of generating functional mast cells from isolated CD34+ cells. Neither Zhang nor Saito, either alone or in combination, expressly or impliedly, teach or suggest any *multistep* culturing procedure where CD34+ cells are cultured in one cytokine mixture *and thereafter* cultured in a different cytokine mixture to generate a population of mast cells. Thus, the obviousness rejection rests on combining the single step procedures described in Zhang and Saito and then comparing it to the claimed method that has been distilled down to its individual steps. This reasoning, however, disregards the "and thereafter" limitation in Claim 37, which is neither taught nor suggested in the combination of Zhang and Saito. By focusing on the individual culturing steps, the Patent Office has not considered all the limitations of Claim 37 and therefore failed to properly consider the claim as whole, as required under MPEP § 2141.02 when determining obviousness. Moreover, there is no teaching or suggestion in the combination of Zhang and Saito that a progenitor cell population derived from CD34+ cells cultured in presence of SCF and flt-3 could even be differentiated into functional mast cells.

Further, in supporting its conclusion, the Patent Office characterizes Zhang's reference to Durand, B. et al. *Blood* 84(11):3667-3674 (1994) as a teaching or suggestion for the use of

expanded progenitor cells for purposes of further differentiation into various mature blood cell types. However, the only remark Zhang makes in regards to the Durand reference is that “SCF and IL-3 was a routine combination in which cells cultured could accelerate engraft.” This statement regarding Durand appears misplaced because the word “engraft” is an art recognized term used to describe the ability of hematopoietic stem cells *in vivo* to repopulate the bone marrow and restore hematopoiesis upon transplantation of cells into a recipient. In contrast, Durand describes an *in vitro* single step culture system of growing isolated CD34+ cells in presence of SCF + IL-3 to sustain the proliferation of cells that differentiate into mast cells. In this regard, Durand is similar to the teachings of Saito, with the only difference being the cytokine combination. As a whole, Zhang’s description is confusing and, at best, inconsistent with the content of Durand. The most logical explanation for the statement is that Zhang is pointing to Durand to reinforce the similarity of results obtained for the same cytokine combination (*i.e.*, SCF + IL-3) in their expansion experiments. Regardless, viewed literally or through the prism of the teachings of Durand, the statement in Zhang would not be interpreted by a skilled artisan as teaching or suggesting the use of expanded progenitor cells prepared in one step as a source of cells for *in vitro* differentiation into functional mast cells in another step.

In view of the foregoing, Applicant submits that the references of Zhang and Saito, either alone or in combination, fail to teach or suggest each and every element of Claim 37. To conclude otherwise would constitute hindsight reconstruction, where parts of the Zhang and Saito references are combined using the Applicant’s disclosure as a blueprint to arrive at the claimed multistep culture method for generating mast cells. This is an impermissible basis for establishing a case of obviousness. See In re Fritsch, 23 USPQ2d 1780 (Fed. Cir. 1992) (“One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.”). Accordingly, the Patent Office has not met its burden of establishing a *prima facie* case of obviousness.

Even if assuming, *arguendo*, that the combination of Zhang and Saito could be read as teaching or suggesting each and every element of the claimed method, an assertion which the Applicant has shown finds no support in the combined references, the finding of a *prima facie* case of obviousness cannot “be predicated on mere identification of individual components of the claimed limitations.” See MPEP § 2143.01. Rather, the references must suggest the

desirability of the combination. See MPEP § 2143.01; see also In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990)). The evidence of a suggestion or motivation to combine may flow from the references themselves, the knowledge of one of ordinary skill in the art, or from the nature of the problem to be solved. It is emphasized that for ascertaining the suggestion or motivation in the cited references, the teachings of the reference must be considered as a whole, including portions that teach away from the claimed invention. See MPEP § 2141.02; see also W.L. Gore & Associates Inc., v. Garlock, Inc., 220 USPQ 303 (Fed. Cir. 1983).

The key argument advanced to support the asserted suggestion to combine the references is that regardless of whether the steps were separated or combined, a significant increase in stem/progenitor cell potential would be expected such that the “combination would enhance mast cell production by one step or two steps.” Yet it is precisely the issue of why a skilled artisan would be motivated to use the claimed method versus a single step method for which the Patent Office has not established an objective rational for justifying a rejection based on *prima facie* obviousness. If a significant increase in the number of progenitor cells occurs “regardless of whether the steps were separated or combined” and that the cytokine “combination would enhance production of mast cells by one step or two,” a skilled artisan would have no motivation to expand progenitor cells using one cytokine combination and then cause the progenitor cells to differentiate into mast cells using another cytokine combination when the one step method would suffice just as well. In fact, out of economy of effort and cost, a person of skill in the art would favor a method with fewer steps (*i.e.*, a single step procedure), as opposed to a method with more steps, when the two methods are considered to produce equivalent results. Based on the rationale asserted to support the obviousness rejection, not only is there no motivation to combine the references, but the combination of references would also clearly teach away from use of a multistep procedure for generating mast cells.

The facts presented by the Patent Office is similar to the situation faced by the Federal Circuit in Winner Int’l Royalty Corp. v. Wang, 53 USPQ2d 1580 (Fed. Cir. 2000). In Winner Int’l Royalty Corp., the patent at issue concerned an automobile antitheft device, known as “The Club,” which is mounted onto the steering wheel and locked in place using a self-locking ratcheting mechanism. Four references were cited against the patent, two of which were considered critical to the obviousness determination. One prior art reference disclosed the same

antitheft device except that it used a deadbolt lock rather than a ratcheting lock. The second prior art reference disclosed an antitheft device that could be folded out when being mounted onto the steering wheel and which was locked into place using a self-locking ratcheting mechanism. The deadbolt lock was more secure but less convenient to use than the ratcheting lock. The Federal Circuit, in upholding the district court's decision of nonobviousness, stated that the lower court did not err when it held that a person skilled in the art would not have elected to trade the "benefit of added security for that of convenience." The Federal Circuit concluded, "[t]radeoffs often concern what is feasible, not what is, on balance, desirable. Motivation to combine requires the latter." See Winner Int'l Royalty Corp., 53 USPQ2d at 1349. Further, the court affirmed the district court's conclusion that the first reference taught away from use of the self-locking ratcheting mechanism, and therefore against the combination of the two references, because the reference had pointed out the susceptibility of the lock to being pried off through exposed grooves in the ratcheting mechanism.

Analogously, in the instant case, there is no suggestion or motivation in the disclosures of Zhang and Saito, either alone or in combination, for the *desirability* of a method that first expands progenitor cells from CD34+ cells and then uses the expanded progenitor cells to generate functional mast cells when a single step method also suffices in generating sufficient numbers of mast cells. Importantly, the asserted efficiency of the single step method for generating mast cells would teach away from use of the claimed multistep culturing process.

For at least the reasons articulated above, Applicant submits that a *prima facie* case of obviousness has not been established for Claim 37. All other claims to which the rejection applies depend from Claim 37. Accordingly, the cited combination fails to render Claims 38, 39 and 42-50 *prima facie* obvious for at least the same reasons. Accordingly, withdrawal of the rejections under 35 U.S.C. § 103(a) is requested with respect to Claims 37-39 and 42-50.

C. Claims 67-70 and 77-80

Claims 67-70 and 77-80 stand rejected as allegedly obvious over Saito et al., *J. Immunol.* 157:343-350 (1996) in view of Zhang, et al., *Chin. J. Biotechnol.* 15:189-94 (1999), and further in view of Demo et al., *Cytometry* 36:340-348 (1999) and Janaki et al., *J. Ethnopharmacol.* 67:45-51 (1999)). The rejection is moot in light of the cancellation of the claims.

VI Rejections Under 35 U.S.C. § 112, ¶ 1

Claims 37-39, 42-53, 56-58, 60-70, and 77-80 stand rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The rejection is moot as applied to cancelled Claims 51-58, 60-70, and 77-80 and traversed with respect to Claims 37-39 and 42-50.

The Patent Office contends that the specification does not adequately enable the types of mast cells produced by the claimed methods. Although Applicant maintains that the mast cells produced are sufficiently enabled, the claims have been amended to recite that the mast cells formed are “functional” mast cells. The amendments are consistent with the Patent Office’s characterization of the mast cells generated by the method, and are fully supported by the disclosure. Cells made by the claimed method display cell differentiation markers and granule proteases (*e.g.*, chymase and tryptase) characteristic of functional mast cells (see, for example, Figures 8 and 9). Importantly, upon stimulation of the IgE receptor, the cells release granule contents histamine, tryptase, and hexosaminidase, and release cytokines IL-5, IL-13, and TNF- α , typical of naturally occurring functional mast cells. As such, a person skilled in the art would have no difficulty in practicing the full scope of the claimed invention. Accordingly, Applicant requests withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

VII Rejoinder of Claims 40 and 41

The restriction requirement in this application was based, in part, on the non-allowability of a generic or other type of linking claim. Under such circumstances, Applicant is entitled to retain claims to the non-elected invention and, if the generic or linking claim is found allowable, to their rejoinder and examination on the merits. See MPEP § 809.04. As such, if Claim 37 is found allowable, Applicant requests withdrawal of the restriction requirement and the rejoinder and examination on the merits of dependent Claims 40 and 41.

VIII Conclusions

Applicant submits that the claims under examination satisfy all of the statutory requirements for patentability and are in condition for allowance. An early notification of the same is kindly solicited. If the Patent Office believes that there are further unresolved issues,

Applicant encourages the Patent Office to contact the undersigned attorney with any questions or concerns by telephone at (650) 494-8700.

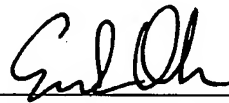
No fees beyond those submitted for filing of the RCE under 37 CFR § 1.17(e) and the Petition for Extension of Time under 37 CFR § 1.17(a) are believed due with this response. However, the Commissioner is authorized to charge any additional required fees, including fees for extensions of time, or credit any overpayment to Dorsey & Whitney LLP Deposit Account No. 50-2319 (File No. 467802-00341; Docket No. A-70882).

Respectfully submitted,

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By: _____



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